ORIGINAL COMMUNICATION

High openness and high extroversion are linked with better time-based prospective memory in multiple sclerosis

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Abstract

Background Prospective memory (PM) deficits are often reported in multiple sclerosis (MS), but their relationship with neuropsychological characteristics and personality traits remains to be explored.

Objective To systematically investigate both time-based and event-based PM abilities in a sample of MS without clinically relevant disability or global cognitive decline and to explore cognitive, neuropsychiatric characteristics and personality traits associated with PM deficits.

Methods Thirty-three patients with MS and 33 healthy individuals were enrolled in the study. All participants underwent a standardized measure of PM to evaluate both time-based and event-based PM. Moreover, patients with MS completed the Brief Repeatable Battery to assess cognitive functioning, the Beck Depression Inventory-II and the Dimensional Apathy Scale to assess neuropsychiatric characteristics, and the NEO Personality Inventory-3 to assess personality traits.

Results Individuals with MS demonstrated impaired time-based PM compared to healthy individuals. The regression analysis showed that poor performance in time-based PM was significantly related to lower extroversion and openness traits, whereas poor performance in event-based PM was significantly related to lower visuospatial memory abilities.

Conclusions Low levels of openness and extroversion traits are associated with a greater risk of developing time-based PM deficit. Therefore, personality assessment and behavioural interventions should be encouraged in MS clinical practice.

Keywords Multiple sclerosis · Prospective memory · Personality · Apathy · Cognitive functioning

Introduction

Prospective memory (PM) is a complex cognitive function that allows to carry out a delayed intended action [1]. According to the prevalent multi-process model, PM involves several phases: (a) forming an intention; (b) associating the intention with a retrieval cue (i.e., time based or event based); (c) retaining this association over an interval that can vary from minutes to weeks, during which the intention representation must be retained; (d) upon noticing the retrieval cue, disengaging from an ongoing task; (e) retrieving the appropriate intention, and (f) properly implementing the intention [2]. Remembering to perform a delayed intention can be triggered by occurrence of an external event (event-based PM) or after a defined amount of time (time-based PM) [1]. Deficits of PM could reduce medication adherence and negatively impact everyday activities such as taking medication in correct dosage at the correct time [3]; therefore, an early identification of deficit of PM seems to be a clinically relevant issue.

Impaired PM abilities occur in neurological diseases characterized by a dysfunction of frontal regions and also in patients with MS when compared with healthy individuals (see review) [4], but several issues remain to be clarified. First, only a few studies investigated separately time-based and event-based PM abilities with mixed results. Miller et al.

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[5] found impairment of time-based but not of event-based PM, whereas Rendell et al. [6, 7] reported deficits of both types of PM abilities. A second aspect to be addressed is the relationships between PM and retrospective memory (RM). Some studies found that patients with MS had deficit of PM without concurrent RM deficits when compared to healthy individuals [6, 8], but other studies reported contrasting findings [9, 10]. Third, only two studies observed an association between executive deficits and poor performance in event-based PM tasks [11, 12], whereas this has been thoroughly investigated in other neurological diseases such as Parkinson's disease [13] or acquired brain injury [14]. Last, although specific personality traits such as high level of conscientiousness were associated with better performance in PM tasks in healthy individuals [15], this issue has not yet explored in MS. Nonetheless, specific personality traits have been reported in MS, consisting of high levels of neuroticism [16, 17], low level of agreeableness, extraversion [16, 17], conscientiousness [16] and openness [16, 18]. Moreover, cognitive deficits in patients with MS have been found associated with distinct personality traits such as high levels of neuroticism [19], and low levels of conscientiousness [17, 19] and openness [19].

Based on these considerations, the current study was designed to achieve three aims: (1) to systematically investigate both time-based and event-based PM abilities in a sample of patients with MS compared to healthy individuals matched for demographic parameters and global cognitive status; (2) to explore whether in MS deficit of event-based and/or time-based PM abilities are associated with impairment of the retrospective component of memory and/or executive dysfunctions; (3) to explore the relationship between personality traits and performance in event-based and time-based PM abilities in MS sample.

Materials and methods

Participants

In the present study, consecutive patients with a diagnosis of MS were recruited at the MS Centre of the Moscati Hospital in Avellino, Italy. To assess PM and personality traits in a relatively homogeneous sample of patients without clinically relevant motor/sensory deficits or global cognitive decline, that could affect participants' responses, each patient had to fulfil the following inclusion criteria to be eligible for the present study: (1) lack of major neurocognitive disorder (according to Diagnostic and Statistical Manual of Mental Disorders 5, DSM 5); (2) lack of general intellectual decline (as defined by an age- and education-adjusted score higher than 15.5 in Montreal Cognitive Assessment, MoCA), (3) mild or moderate disability (as indicated by a score lower

than 7 in the Expanded disability Status Scale, EDSS), (4) no previous psychiatric illness, head trauma, neurological diseases or alcohol or drug abuse. For each patient, we recorded the following clinical aspects: disease duration, age at onset, current pharmacological treatment and EDSS. After recruitment of MS patients, we selected a sample of healthy individuals (HCs) with demographic features as similar as possible to those of the patients. HCs were included if they met the following criteria: (1) lack of history of MS or other neurological diseases; (2) lack of familiarity for MS in first-degree relatives; (3) lack of previous or current psychiatric diseases (e.g., major depression, or psychosis according to DSM-5 criteria); (4) no use of psychoactive drugs.

The study was performed in accordance with the ethical standards of the 1964 Helsinki declaration and was approved by local ethics committee. All participants gave their written informed consent to participate on a voluntary basis.

Materials and procedures

Patients with MS and HCs underwent the Italian version of the MoCA to assess global cognitive functioning and the Memory for Intentions Screening Test (MIST) to evaluate PM abilities. The MIST is a standardized test requiring delayed execution of intended actions to be performed in the context of an ongoing foreground task. It has been translated into Italian other than into English, but normative data in an Italian population sample are still lacking. It is composed of eight PM tasks balanced for delay interval, cue (time or event based), and response modality (verbal or motor response). Additionally, participants complete a three-choice recognition task for cue–target association immediately after completion of the MIST (recognition task). Lastly, to obtain a 24-h probe, participants were instructed to leave a telephone message for the examiner the following day specifying the number of hours slept the night after the assessment (24-h item).

To assess perceived problems concerning both prospective and retrospective memory, patients with MS and HCs completed the Prospective and Retrospective Memory Questionnaire (PRMQ), a 16-item questionnaire with 8 questions about the frequency of retrospective memory failures and the other 8 pertaining to PM failures. The items were rated on a 5-point scale ranging from 1 (never) to 5 (very often).

To evaluate the cognitive correlates of PM abilities in MS, patients (but not HCs) underwent the version A of the Rao's Brief Repeatable Battery (BRB), exploring verbal memory and delayed recall [Selective Reminding Test (SRT) and SRT-Delayed Recall (SRT-D)], visuospatial memory and delayed recall [10/36 Spatial Recall Test (10/36-SPART) and 10/36 SPART-Delayed Recall (10/36 SPART-D)], concentration, sustained attention and information proceeding speed [Paced Auditory Serial Addition Test at 3 s

(PASAT 3″) and at 2 s (PASAT 2″), Symbol Digit Modalities Test (SDMT)], and verbal fluency in semantic stimulus [Word List Generation (WLG)]. Executive functions were also assessed by the Stroop Color-Word Interference Test (SCWIT), which mainly investigates inhibitory control.

To evaluate the neuropsychiatric correlates of PM abilities, all patients (but not HCs) completed: the Italian version of Beck Depression Inventory-II (BDI-II) that consists of 21 items scored on 4-point Likert scale with higher scores reflecting higher levels of depression; and the Italian version of the Dimensional Apathy Scale (DAS) consisting of 24 items scored on 4-point Likert scale, ranging from 'hardly ever' to 'almost always' with higher scores indicating more severe apathy.

Last, to evaluate the personality traits related to PM abilities, patients (but not HCs) completed the Italian version of the NEO Personality Inventory-3 (NEO-PI-3), consisting of 240 items to be answered on a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree'. Items are grouped in the following scales: neuroticism, extraversion, openness, agreeableness, and conscientiousness. The references of diagnostic criteria for MS, and the clinical and neuropsychological tools are reported in Supplemental Material 1.

Statistical analysis

Comparisons between patients with MS and HCs based on the demographic and cognitive variables recorded in both groups were performed by multivariate analysis of variance (MANOVA).

Within MS group only, to investigate which factors contributed to performance in time-based and event-based PM abilities, we performed two separate stepwise linear regression analyses. In the first analysis, we entered the score of MIST time-based task as the dependent variable, whereas in the second the score of the event-based task was entered as the dependent variable.

Prior to performing the regression analyses, we grouped cognitive tasks into four domains: verbal learning and memory (SRT, SRT-D), visuospatial learning and memory (10/36-SPART; 10/36-SPART-D), attention–executive (PASAT 3″, PASAT 2″, SDMT), fluency. Then, we calculated Z scores for each cognitive domain (averaging Z scores for cognitive tasks included in each domain) [20, 21].

In both analyses, the same independent variables were entered in blocks: personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) in block 1; cognitive domains (verbal learning and memory, visuospatial learning and memory, attentional–executive domain, fluency) in block 2; and neuropsychiatric variables (BDI-II, DAS) in block 3. The critical alpha level for all

analyses was set at 0.05. Analyses were performed with SPSS program.

Results

Participants

After excluding 11 patients (4 patients for a global cognitive decline, 5 for severe disability, 2 for neurological comorbidities), we included 33 patients with MS (20 females) and 33 HCs (22 females) in the study (Table 1). Among patients with MS, 28 patients had remitting relapsing MS and 5 secondary progressive MS. Eleven patients were treated with interferon beta 1a, 1 with interferon beta 1b, 3 with glatiramer, 6 with fingolimod, 3 with dimethyl fumarate, 3 with teriflunomide, and 6 patients received no treatment. The two groups did not differ based on the demographic variables (Table 1).

Neuropsychological assessment

MANOVA showed that the two groups differed significantly from each other (Wilks' lambda = 2.01; $p = 0.036$; $\eta_p^2 = 0.40$). The analysis identified significant differences between the two groups for two measures of MIST, as patients with MS performed significantly worse than HCs in time-based PM task ($F = 8.74$; $p = 0.004$; $\eta_p^2 = 0.131$) and in recognition task ($F = 7.76$; $p = 0.007$; $\eta_p^2 = 0.118$), but not in event-based PM task ($F = 3.6$; $p = 0.063$; $\eta_p^2 = 0.074$) and 24-h item ($F = 2.19$; $p = 0.144$;, $\eta_p^2 = 0.036$; see Table 1).

Personality, neuropsychiatric and cognitive variables associated with prospective memory in MS

The regression analysis for identifying factors associated with time-based PM abilities showed that poor performance was significantly related with lower scores in extroversion (Beta = 0.61, $t = 4.38$, $p < 0.001$; 95% CI 0.038–0.104) and openness subscales (Beta = 0.48, $t = 3.47$, $p = 0.002$; 95% CI 0.022–0.087) and lower attentional–executive domain score (Beta = 0.42, $t = 2.72$, $p = 0.012$; 95% CI 0.205–1.481). No other variables were significantly related to time-based PM task (Beta ≤ 0.26, $t ≤ 1.66$, $p ≥ 0.110$).

The regression analysis for identifying factors associated with event-based PM abilities showed that poor performance was significantly related to lower visuospatial learning and memory domain score (Beta = 0.55, $t = 3.97$, $p = 0.001$; 95% CI 1.340–4.269). No other variables were significantly related to event-based PM task (Beta ≤ 0.23, $t ≤ 1.46$, $p ≥ 0.158$).

Table 1 Comparison between multiple sclerosis patients and healthy subjects based on demographic and cognitive variables (mean ± standard deviation)

Demographic variables	Patients ($n=33$)	Healthy subjects ($n=33$)	F	p	η_p^2
Age	44.60 ± 13.02	40.06 ± 11.86	2.000	0.163	0.033
Education	12.28 ± 4.60	14.15 ± 2.64	3.836	0.055	0.062
Clinical variables					
EDSS	4.57 ± 5.74	–			
Duration of disease (months)	115.26 ± 74.89	–			
Age at onset of disease (years)	33.82 ± 11.01	–			
Cognitive variables					
MOCA	23.78 ± 3.62	25.53 ± 2.78	3.357	0.072	0.071
Total MIST	28.75 ± 12.16	38.06 ± 8.09	12.467	0.001*	0.177
Total time based	4.57 ± 1.91	5.87 ± 1.49	8.742	0.004*	0.131
Total event based	5.60 ± 2.61	6.81 ± 1.67	3.600	0.063	0.074
Recognition	7.35 ± 0.95	7.87 ± 0.42	7.761	0.007*	0.118
24 h	0.82 ± 0.94	1.18 ± 0.96	2.191	0.144	0.036
PMRQ-PM	23.46 ± 8.43	19.81 ± 5.87	3.866	0.054	0.062
PMRQ-RM	20.96 ± 6.10	17.43 ± 4.69	6.387	0.014*	0.099
SRT	43.55 ± 11.41	–			
SRT-D	6.08 ± 2.96	–			
10/36 SPART	19.85 ± 5.02	–			
10/36 SPART-D	6.02 ± 2.27	–			
PASAT 3″	34.15 ± 19.25	–			
PASAT 2″	29.12 ± 15.12	–			
SDMT	45.06 ± 15.62	–			
WLG	20.82 ± 5.73	–			
SCWIT	87.79 ± 60.62	–			
Personality variables					
NEO-PI N	59.65 ± 6.29	–			
NEO-PI E	44.38 ± 8.85	–			
NEO-PI O	45.97 ± 10.85	–			
NEO-PI A	44.79 ± 9.92	–			
NEO-PI C	51.58 ± 10.76	–			
Neuropsychiatric variables					
DAS	27.51 ± 9.58	–			
BDI-II	18.53 ± 13.65	–			

MOCA Montreal Cognitive Assessment, *MIST* Memory for Intentions Screening Test, *EDSS* Expanded Disability Status Scale, *PMRQ* The Prospective and Retrospective Memory Questionnaire; *STR* Selective Reminding Test, *STR-D* Selective Reminding Test-Delayed Recall, *10/36 SPART* 10/36 Spatial Recall Test, *10/36 SPART-D* 10/36 Spatial Recall Test-Delayed Recall, *PASAT 3″* Paced Auditory Serial Addition Test at 3 s, *PASAT 2″*, Paced Auditory Serial Addition Test at 2 s, *SDMT* Symbol Digit Modalities Test, *WLG* Word List Generation, *SCWIT* Stroop Color-Word Interference Test, *NEO-PI* NEO Personality Inventory, *N* neuroticism, *E* extraversion, *O* openness, *A* agreeableness, *C* conscientiousness, *BDI-II* Beck Depression Inventory-II, *DAS* Dimensional Apathy Scale

*$p < 0.05$

Discussion

The present study showed that individuals with MS had a specific pattern of impairment in PM, as they performed worse than HCs in the time-based PM task and in the recognition task (not in the event-based PM tasks), and that different variables, including some personality traits, were related to time- or event-based PM.

The poorer performance of MS patients in time-based but not in event-based PM task with respect to HCs, consistent with some previous studies [5, 22], might be related to the differences in cognitive requirements of the two PM tasks. Event-based PM would require relatively automatic processes rather than strategic resource-demanding monitoring, because it relies on detection of salient external cues [23, 24]. Time-based PM task, instead, would entail more

strategic and self-initiated strategies than event-based PM, as individuals have to monitor the passage of time to initiate the action [23, 24]. To successfully perform a time-based PM task, individuals continue looping through 'test-wait' cycles until a test is made during a critical period [25]. As correct performance is dependent on monitoring/checking time during a critical period [26], patients with MS could have a selective impairment in time monitoring and time estimation. Indeed, executive abilities, and in particular monitoring, are thought to be associated with prefrontal functioning that would be highly vulnerable in MS [27].

However, patients with MS achieved lower scores than HCs in the MIST recognition task too. This is a novel finding, as the only study using MIST did not report differences between MS and HCs in this task [5]. Classically, the recognition task is thought to assess the retrospective memory component of PM (i.e., encoding, retention, and retrieval of intentions) and impairment in this task might suggest an encoding/memory deficit [22].

The main findings of the present paper consist of the observation that poor performance in time-based PM was related to low scores in two personality traits, i.e., extroversion and openness, and to low performance in attentional–executive tasks. Poor performance in event-based PM task was only related to low performance in visuospatial learning and memory tasks. The novel finding of the correlation of time-based PM with lower scores in extraversion and openness trait personality traits would suggest a role for cognitive reserve [28], an indicator of resilience to cognitive decline in neurodegenerative diseases [29], in protecting patients with MS from decline of PM. It has been argued that higher openness and extroversion traits would be related to use of memory strategies (e.g., setting an alarm or using a clock) [30], for effective recall of future plans for participating in social life [31], and would pose a high demand on executive functions, such as inhibition and set shifting, that are involved in time-based PM [15, 31, 32]. Higher levels of openness and extraversion would be positively related with stimulating and cognitively enriching activities in lifetime, i.e., a larger cognitive reserve that would lead to reduced PM failures in everyday life [33].

The significant association between executive functioning with time-based PM performance was consistent with previous studies [34, 35]. Executive functions play a key role in time-based PM tasks that require self-monitoring and self-initiated strategies, as recalled above [36]. Indeed, it has been argued that patients with MS and executive dysfunctions would strongly depend on distinctiveness/salience of cue in PM task performance, thereby being particularly impaired when external cues are not available, i.e., in time-based tasks [11].

The personality trait and cognitive variables that showed a significant independent relation with time-based PM did not significantly affect event-based PM. Visuospatial learning and memory were the only cognitive variables significantly associated with performance in event-based PM task that was relatively well preserved. This finding would suggest that in our MS sample, better visuospatial encoding and retrieval abilities would have positive effects on encoding the intention, forming an association between the specific visuospatial context and the intention, and later retrieving it during the delayed performance interval [37].

Finally, our result showed that subjective evaluation of PM in MS would be less reliable than objective assessment by means of specific tasks. Indeed, PRMQ did not differ between patients with MS and HCs and did not correlate with MIST total or subtasks scores [4]. Thus, self-reported questionnaires of PM evaluation are easier to administer but would have limited value in searching for PM impairment in MS.

To the best of our knowledge, this is the first study investigating personality traits associated with PM in MS. For this reason, our research method and data analysis approach could be considered as exploratory and findings should be treated with caution because of several possible limitations. First, we could assess only a relatively small sample of patients who accepted to undergo a thorough evaluation of their personality traits. Moreover, it should be considered that we only recruited patients without clinically relevant disability or global cognitive decline to avoid the role of factors potentially affecting assessment of personality traits and PM. The features of our small patient sample limited the possible generalization of our findings. Second, we used a PM test that has been translated in Italian but not properly validated. Although we only used the MIST to compare the two groups, it is important to consider that its cross-cultural validity and the psychometric properties of its Italian version have not been established yet. Third, the present study did not assess time estimation abilities, which are involved in time-based PM task together with cognitive flexibility and monitoring. Lastly, we focus our regression analysis only in patients with MS and did not carry out a similar analysis in healthy individuals. Therefore, as we assessed neuropsychiatric characteristics and personality traits in patients with MS only, our study could not clarify whether the relationships between these variables, in particular personality traits, and PM could be specific to MS or reflect a general phenomenon that could be present in healthy population too. Nonetheless, our findings could be of interest and suggest that factors beyond that of cognitive functioning should be considered in clinical assessment of MS.

In conclusion, we observed that some personality traits would be closely related to time-based but not to event-based PM in patients with MS not affected by clinically relevant motor disability and global cognitive decline. In particular, patients with low levels of openness and extroversion traits

seem to have a greater risk of developing PM deficit. Our findings warrant future longitudinal research to clarify how personality traits affect PM functioning and to encourage personality assessment and behavioural interventions in MS.

Compliance with ethical standards

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